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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/468,145	06/06/1995	JURGEN ENGEL	Y17506/93-11	4889

909 7590 07/10/2002

PILLSBURY WINTHROP, LLP
P.O. BOX 10500
MCLEAN, VA 22102

EXAMINER	
MINNIFIELD, NITA M	
ART UNIT	PAPER NUMBER
1645	40

DATE MAILED: 07/10/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Offic Action Summary	Application No. 08/468,145	Applicant(s) ENGEL ET AL.	
	Examiner N. M. Minnifield	Art Unit 1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 April 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *39* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Response to Amendment

1. Applicants' amendment filed April 22, 2002 is acknowledged and has been entered. Claim 23 has been amended. New claim 24 has been added. Claims 20-24 are now pending in the present application. All rejections have been withdrawn in view of Applicants' amendment and/or arguments, with the exception of those discussed below.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. Claims 20-23 (and now claim 24) are rejected under 35 U.S.C. 103(a) as being unpatentable over Wolf et al (DD 411996) taken with Behre et al (1992).

The claims are directed to a method for the preparation of a sterile Cetrorelix lyophilizate, said method comprising the steps of dissolving the Cetrorelix in aqueous acetic acid to form a solution, diluting the solution with water, adding a bulking agent (hexitol, mannitol, etc), sterile filtering, dispensing into injection vials and lyophilizing the solution, thereby obtaining a sterile Cetrorelix lyophilizate; 3% solution and pH of 2.5-3.0.

Wolf et al teach methods of preparing lyophilized synthetic LHRH, which preparation is stable at room temperature over a long period of time (page 1 of English translation; p. 3-4). Wolf et al teach the use of vehicle (i.e. mannitol; bulking agent) and buffer (i.e. acetic acid) substance for the adjustment of an optimal range of the hydrogen-ion concentration, pH (p. 2; p. 4). The prior art

teaches that the application can be for veterinary medicine as an estrus-synchronization agent as well as *inter alia* in the human medicine as an agent in the case of treating fertilization disorders (p. 2-3). Wolf et al teach sterilization by filtration and that the solution is lyophilized (p. 5). The prior art teaches the claimed invention except for the specific preparation of Cetrorelix lyophilizate.

However, Behre et al teach that GnRH antagonist Cetrorelix (an antagonistic analog of GnRH) has the potential for treatment of sex hormone-dependent diseases and male contraception (abstract). Behre et al teach the use of Cetrorelix in lyophilized for injection and was dissolved in water containing mannitol (p. 394).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to use a drug or compound similar to LHRH/GnRH to treat infertility in humans or veterinary medicine. The art teaches the method of preparing the LHRH, which is similar to the Cetrorelix, an antagonistic analog of LHRH/GnRH. The Cetrorelix is a small peptide similar to LHRH and Wolf et al teaches the same method in preparing the sterile LHRH lyophilizate as claimed by Applicants, using the bulking agent (mannitol), a buffer (acetic acid) and sterile filtering, and lyophilizing the solution. Both the prior art (in combination) and the claimed invention prepare the cetrorelix (sterile and lyophilized) for the same purpose and in the same manner. The claimed invention is prima facie obvious in view of the prior art, absent any convincing evidence to the contrary.

The rejection is maintained for the reasons as set forth above. Applicant's arguments filed April 22, 2002 have been fully considered but they are not persuasive.

It is noted that the effective filing date for the pending application is February 19, 1993. Reissmann et al (1994) and Diedrich et al (1994) have been removed as references in this 103 obviousness rejection.

Claims 20-23 (and now claim 24) are rejected under 35 U.S.C. 103(a) as being unpatentable over Wolf et al (DD 411996) taken with Behre et al (1992).

Applicants have asserted that the claims are directed to a method of preparing a sterile Cetrorelix lyophilizate with a specific decapeptide formula (see p. 4 of the amendment). However, this formula is not set forth in the claims. It appears the Behre et al teaches this formula (see p. 393 and materials and methods). The claims recite "method for the preparation of a sterile Cetrorelix lyophilizate...". The prior art in combination (Wolfe et al taken with Behre et al) sets forth this method and the cetrorelix lyophilizate. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., cetrorelix dissolved in 30% acetic acid or final strength of 3%) are not recited in the rejected claims 20-22. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Applicants have asserted that the art uses buffering agents to maintain the lyophilizate stability, which the claimed invention does not employ. However, Wolfe et al uses acetic acid, the same as Applicants. Further, claims 20-22 do not recite

a specific pH. Applicants have asserted that the prior art does not recognize the importance of dissolving decapeptides having terminal amide functions in aqueous acetic acid to form a solution, and them diluting the solution with water for injection to avoid retention of the peptide in filters. Wolfe et al teaches the use of water in the solution and acetic acid as well as mannitol (p. 4), which are components in Applicants' claims. Applicants have asserted that Behre et al is silent with respect to improving filterability of the cetrorelix solution and does not teach the dissolution of decapeptides having terminal amide functions in aqueous acetic acid to form a solution, and then diluting the solution with water for injection to avoid retention of the peptide in filters. It is noted that Behre et al is cited to show that cetrorelix is an LHRH antagonist and that it can be prepared in the same manner as the LHRH. Behre et al uses a lyophilized cetrorelix dissolved in water and contains mannitol (p. 393; materials and methods). Further, it is noted that Applicants are arguing limitations (avoiding retention of the peptide in filters) that are not set forth in the claims.

The prior art of Wolfe et al taken with Behre et al teaches the claimed invention except for specific cetrorelix concentration of 3% and the specific pH range of 2.5 to 3.0. It would have been obvious to one having ordinary skill in the art at the time the invention was made to determine the most appropriate cetrorelix concentration to avoid clogging up the filters and the determine the correct pH range for a stable buffered solution, since it has been held that discovering an optimum value of a result effective variable involves only routine skill in the art. In re Boesch, 617 F.2d 272, 205 USPQ 215 (CCPA 1980).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and In re Jones, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the art teaches the method of preparing the LHRH, which is similar to the Cetrorelix, an antagonistic analog of LHRH/GnRH. The Cetrorelix is a small peptide similar to LHRH and Wolf et al teaches the same method in preparing the sterile LHRH lyophilizate as claimed by Applicants, using the bulking agent (mannitol), a buffer (acetic acid) and sterile filtering, and lyophilizing the solution. Both the prior art (in combination) and the claimed invention prepare the cetrorelix (sterile and lyophilized) for the same purpose and in the same manner. The claimed invention is prima facie obvious in view of the prior art, absent any convincing evidence to the contrary.

The unexpected and novel aspects of the invention should be set forth in the claims, preferably the independent claim, that distinguish the claimed invention over the prior art.

4. No claims are allowed.

5. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to N. M. Minnifield whose telephone number is 703-305-3394. The examiner can normally be reached on M-F (8:00-5:30) Second Friday Off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette R.F. Smith can be reached on 703-308-3909. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4556 for regular communications and 703-308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

N. M. Minnifield
Primary Examiner
Art Unit 1645

July 3, 2002